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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,440	01/19/2000	DAVID PHILIP LANE	MEWB25.001AP	7276

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/403,440	LANE, DAVID PHILIP	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/12/06;10/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 3, 11.

Accordingly, claims 1, 2, 8 are being examined.

Objection

Claims 1-2, 8 remain objected to for the use of the language "mdm2" as the sole means of identifying the protein for use in the claimed method, for reasons already of record in paper of 10/20/05.

Applicant argues that similar to p53, mdm2 is well known, and generally used name for a known protein, such as in the references cited on pages 36-38 of the instant application, and references cited by the Examiner. Applicant recites WO 93/20238, in which a cDNA sequence of human mdm2 is recited. Applicant argues that there can be absolutely no doubt that they refer to the same protein.

This is not found to be persuasive. Different from p53, mdm2 is not a well known protein. Although several references use the name mdm2, different laboratories may use the same laboratory designations to define completely distinct proteins. Amendment of the claims to include physical and/or functional characteristics of "mdm2", which unambiguously define "mdm2", for example, a sequence identification number, is required.

NEW REJECTION NECESSITATED BY THE AMENDMENT

Claim Rejections - 35 USC § 103

Claims 1-2, 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bottger et al, 1996 (Oncogene, 13: 2141-2147, of record), in view of McCann A H et al, 1995 (British J Cancer, 71(5): 981-5, of record), and further in view of Lee JM et al, 1995 (Cancer and metastasis Review, 14(2): 149-161, of record).

Claim 1 is drawn to an in vitro method for disrupting the binding of p53 and mdm2 in a population of cancer cells in which mdm2 is not overexpressed, comprising administering a peptide, less than 25 amino acids in length, and comprising SEQ ID NO:3.

Claim 2 is drawn to the method of claim 1, wherein the p53 is activated for DNA specific binding and transcription.

Claim 8 is drawn to the method of claim 1, wherein the peptide has the property of competing with mdm2 for binding p53, but does not inhibit DNA specific binding property of p53.

It is noted that SEQ ID NO:3 (or TIP 12/1) of the instant application corresponds the 19 amino acids portion of the wild type mdm2 binding site of p53 (TIP), amino acids P13 to N29 of wild type p53 (the instant application, p.24, paragraph before last), except that its core wild type p53 peptide QETFSDLWKLLP is replaced with the amino acids M**P**RFMD**Y**WEGLN.

Bottger et al teach the consensus sequence **P**XFXD**Y**WXXL contained in the 12 amino acid peptide M**P**RFMD**Y**WEGLN (Table 1 on page 2142). It is noted that the 12 amino acid peptide M**P**RFMD**Y**WEGLN taught by Bottger et al is the same as the peptide M**P**RFMD**Y**WEGLN of the claimed invention, which is a 12 amino acid fragment of the 19

amino acid peptide SEQ ID NO:3 of the claimed invention. Bottger et al teach that the 12 amino acid peptide M**P**RFM**DY**WEGLN, corresponding the wild type p53 peptide QET**FSDLWKLLP** from the mdm2 binding site on human p53, is superior than said wild type p53 peptide, and is important for maximum strength of interaction with hdm2, significantly increasing the inhibitory activity of the peptide against the binding of the wild type p53 and mdm2 (abstract, p. 2141, second column, first paragraph, figure 5 on page 2144, table 1 on page 2142, p.2144, and p.2146, second column, paragraph under peptides and monoclonal antibodies). It is noted that the mdm2 binding site of the p53 amino acid sequence is well known in the art, as evidenced by the 19 amino acid sequence from the mdm2 binding site on wild type human p53 recited by Bottger et al on Table 1 on page 2142, and the teaching of Bottger et al that the N-terminal region of p53 is important for its interaction with mdm2, as shown by deletion and mutational studies by Oliner et al, 1993 (Bottger et al, p. 4141, second paragraph, lines 18-20). Bottger et al also teach that the amino acids Proline and Tyrosine from the peptide 12/1 are selected by phage display as additional binding points for hdm2, for improved stability of the peptide, and for its better conformational fit into the hdm2 binding pocket of p53, to displace the binding of p53 to hdm2 (p.2144, second column, last four lines of the third paragraph). Bottger et al teach that the oncogene mdm2 and its human homologue hdm2 bind to the tumor suppressor protein p53 and inactivates p53 function as a positive transcriptional factor, i.e. a natural modulator of p53 function, and that the mdm2-p53 interaction is a much persued target for the development of anti-cancer drugs (abstract). Bottger et al further teach that the peptide represents a clear route towards the design of small synthetic molecules that will restore p53 function in human tumors

(p.2141, second column, first paragraph), in view that mdm2 binds to p53 and inactivates its function as a transcriptional factor (p.2141, first column).

Bottger et al do not teach SEQ ID NO:3. Bottger et al do not teach an in vitro method for disrupting the binding of p53 and mdm2 in a population of cancer cells in which mdm2 is not overexpressed comprising administering a peptide, less than 25 amino acids in length, and comprising SEQ ID NO:3. Bottger et al do not teach that the p53 is activated for DNA specific binding and transcription, or that the peptide has the property of competing with mdm2 for binding p53, but does not inhibit DNA specific binding property of p53.

McCann et al teach that protein expression of mdm2 in breast carcinoma is significantly associated with low level of p53, and of note is the fact that most of these mdm2 tumors have no mdm2 gene amplication (abstract, lines 7-9, p.983, first column, last paragraph, last 7 lines). McCann et al teach that mdm2 amplification only occurs at a low frequency in breast cancer, as compared to non-epithelial tumors (abstract, p.983, p.984, first column, first two lines of third paragraph, and table II on page 983).

Lee et al teach that p53 could induce apoptosis and cell cycle arrest, and that loss of p53 function causes increased resistance to chemotherapeutic agents (abstract). Lee et al teach that p53 functions as a transcriptional factor, via binding to specific DNA (p. 150).

It would have been prima facia obvious to make a peptide from the mdm2 binding site of p53, wherein said peptide comprises the 12 amino acid peptide M**P**RFM**DY**WEGLN taught by Bottger et al, and wherein said peptide is of larger size than the 12 amino acid peptide taught by Bottger et al to increase the stability of the peptide, because additional wild type p53 amino acids surrounding the peptide M**P**RFM**DY**WEGLN taught by Bottger et al are part of the mdm2

binding site of wild type p53, and thus would further add to the stability of the peptide by increasing the size of the peptide. It would have been obvious to use the peptide comprising the 12 amino acid peptide M**P**R**F**M**D****Y**W**E**G**L**N taught by Bottger et al to target cancer cells that express p53 and mdm2 to increase p53 function, including those populations of cancer cells that do not overexpress mdm2, such as in breast cancer cells, taught by McCann et al, because loss of p53 function is correlated with increased resistance to chemotherapeutic agents, as taught by Lee et al, and because hdm2 binding to the tumor suppressor protein p53 has been known to inactivate p53 function, and it is desirable to design synthetic peptides that interfere with the mdm2-p53 interaction and restore p53 function in human tumors that as taught by Bottger et al, and because in cancers which do not overexpress mdm2, such as breast cancer cells, the protein expression of mdm2 is significantly associated with low level of p53, as taught by McCann et al.

One would have expected that the peptide taught by the combined art would disrupt the binding of p53 and mdm2 in tumor cells, and increase the activity of p53, because the consensus sequence **P**X**F**X**D****Y**W**X**X**L** contained in the peptide significantly increases the inhibitory activity of the peptide against the binding of the wild type p53 and mdm2, as taught Bottger et al, and because hdm2 binding to the tumor suppressor protein p53 has been known to inactivate p53 function, as taught by Bottger et al.

One would have been expected that the peptide does not inhibit the DNA specific binding property of p53, because the peptide taught by the combined art would disrupt the binding of p53 to mdm2 by binding **only** at the specific p53 binding site for mdm2, as taught by Bottger et al, which is different from the DNA binding site of p53. One would have expected that that p53 is

activated for DNA specific binding and transcription, because the activity of p53 is to function as a transcriptional factor, via binding to specific DNA , as taught by Lee et al and Bottger et al .

Answers to Applicant's Arguments

Claim Rejections - 35 USC § 103

Applicant argues that there is nothing in the cited references which suggest the claimed invention, because the prevailing theory was that overexpression of mdm2 interferes with the normal feedback loop between mdm2 and p53, allowing cells that overexpress mdm2 to escape from p-53 regulated growth control by binding p53 (see specification, p.1, last para bridging p.2). Applicant argues that thus one would not have motivation to try to inhibit the binding of mdm2 and p53 in cancer cells not overexpressing mdm2, because based on prevailing theory, such inhibition would not have been expected to provide any clinical benefit. Applicant argues that even if such motivation had existed, one would not have expected that such inhibition on cells not overexpressing mdm2 would activate p53 function. Applicant argues that the claimed invention uses the peptide comprising SEQ ID NO:3 and not the peptide taught by Bottger et al.

Applicant's arguments in paper of 04/18/06 have been considered but are found not to be persuasive for the following reasons:

It is noted that in the specification, p.1, last para bridging p.2, only one reference is recited, WO 93/20238. A single cited reference does not constitute the prevalent theory at the time the invention was made. Further, WO 93/20238 does not teach or suggest that mdm2 does not suppress p53 in cancer cells that do not overexpress mdm2. WO 93/20238 only discloses that overexpression of mdm2 in some tumor cells interferes with normal feedback loop between

mdm2 and p53, allowing cells that overexpress mdm2 to escape from p-53 regulated growth control by binding p53. On the contrary, at the time the invention was made, McCann et al teach that protein expression of mdm2 in breast carcinoma is significantly associated with low level of p53, and of note is the fact that most of these mdm2 tumors have no mdm2 gene amplication (abstract, lines 7-9, p.983, first column, last paragraph, last 7 lines). In other words, the teaching of McCann et al clearly shows that p53 is suppressed in cancer cells such as breast cancer cells, a majority of which does not overexpress mdm2, which p53 suppression is correlated with the presence of mdm2. Further, Bottger et al teach that the mdm2-p53 interaction is a much persued target for the development of anti-cancer drugs (abstract), and that the peptide represents a clear route towards the design of small synthetic molecules that will restore p53 function in human tumors (p.2141, second column, first paragraph), in view that mdm2 binds to p53 and inactivates its function as a transcriptional factor (p.2141, first column). Thus the cited references clearly provide motivation for using a peptide inhibitor of mdm2 and p53 interaction, for treating those cancer cells that do not overexpress mdm2, because in these cancer cells, the level of p53 is low, and is associated with the expression of mdm2, as taught by McCann et al.

Moreover, it would have been obvious to use a peptide comprising SEQ ID NO:3, because SEQ ID NO:3 contains the 12 amino acid peptide taught by Bottger et al having the consensus sequence PXFXDYWXXL, which is important for maximum strength of interaction with hdm2, and significantly increases the inhibitory activity against the binding of the wild type p53 and mdm2, as compared to the corresponding wild type p53 sequence QETFSDLWKLLP, as taught by Bottger et al, and because additional N- and C-terminal wild type p53 amino acids surrounding the peptide MPRFMDYWEGLN taught by Bottger et al are part of the mdm2

binding site of wild type p53, and thus would further add to the stability of the peptide by increasing the size of the peptide.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

July 05, 2006

JEFFREY SIEW
SUPERVISORY PATENT EXAMI